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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/805,290	03/13/2001	Sandra Bezemer	F7526(V)	1258

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/805,290	BEZEMER ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-12* is/are pending in the application.

4a) Of the above claim(s) *6-8,11 and 12* is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,9 and 10* is/are rejected.

7)☒ Claim(s) *5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 1/29/07 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group I (claims 3-5), and species of SEQ ID NO: 8 as the CDR3 species and SEQ ID NO: 19 as the antibody/fragment in Applicant's response filed 7/21/04.

Claims 6-8, 11 and 12 (non-elected Groups II-VI) remain withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions. (It is noted by the Examiner that withdrawn claim 6 depends upon a canceled claim, withdrawn claim 7 depends upon claim 6, and withdrawn claim 8 depends upon claim 7).

Applicant is reminded that upon consideration of a search of the prior art, the search had been extended to include SEQ ID NO: 8-26.

Claims 1, 4, 5, 9 and 10 are currently being examined.

The following are new grounds of rejection necessitated by Applicant's amendment filed 1/29/07.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 4, 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of: (1) the claimed antibody or fragment thereof that binds specifically to a human pancreatic lipase and wherein the antibody or fragment thereof of comprises a variable domain derived from an immunoglobulin naturally devoid of light chains, and food product thereof or pharmaceutical composition thereof, recited in the instant claims, (2) the claimed antibody or fragment thereof recited in instant claim 4 wherein the antibody

or fragment thereof that binds one or more human pancreatic lipases comprises 3 CDR regions, whereby CDR3 is one of the recited SEQ ID NO and wherein the antibody or fragment thereof of comprises a variable domain derived from an immunoglobulin naturally devoid of light chains, and the antibody or fragment thereof is not one of the full length antibody sequences or antigen binding fragments thereof of the SEQ ID NO recited in instant claim 5.

The instant claims encompass: an antibody or fragment thereof that specifically binds human pancreatic lipase and comprises a CDR3 from the sequences recited in instant claim 4 and has undisclosed other portions that may not be CDR1 and CDR2, or that comprises some domain from a heavy chain variable region as recited in instant claim 1 that may or may not be a CDR. There is insufficient disclosure in the specification on such an antibody/fragment/functional equivalent/composition thereof wherein the antibody or fragment comprises a heavy chain variable domain derived from an immunoglobulin naturally devoid of light chains, wherein the entire variable region of a V_HH antibody consisting of CDR1, CDR2 and CDR3 is not present.

The specification discloses that it is desirable to decrease the level of LDL and that several dietary enzymes may be involved in the hydrolysis reaction that liberates fatty acids in the GI tract to increase the adsorption of cholesterol by the epithelium (page 1). The specification discloses that other enzymes in the GI tract may be involved in undesirable physiological reactions and examples of such enzymes, referred to as human dietary enzymes, include oxidoreductases, transferases, hydrolases (*e.g.,* lipases, proteolytic enzymes and ureases), lyases, isomerases and ligases or synthetases (page 2 at lines 1-5). The specification discloses that human pancreatic lipase (HPL) was purified, used as an immunogen to generate V_HH antibodies in a llama, and V_HH fragments that inhibited HPL were cloned, selected, screened, enriched, a portion were sequenced, and the V_HH were grouped into three classes depending upon the length of CDR3 (pages 15-24). The specification further discloses that a number of these were re-cloned and purified (pages 25-26). The specification discloses parallel work for production of V_HH antibodies to human gastric lipase (HGL) (pages 28-32). The specification discloses feeding the antibodies HPL18 and HGL8 to piglets in combination with a high fat diet, and that in 2/3 animals, the antibodies inhibited fat digestion and uptake as evidenced by a reduction in blood triglyceride levels (pages 33-36). The specification further discloses that the V_HH antibodies are used for the inhibition, or in the case of human dietary lipases for partial inhibition, of the enzymes involved in the hydrolysis of dietary fats (pages 8 at lines 28-31, page 9 at lines 23-30 and the brief description of the drawings for Figures 1-3, figures 1-3).

The specification does not disclose antibodies comprising just a CDR3 region peptide recited in instant claim 4 without the corresponding other CDR1 and CDR2 regions, including those that accompany them in the intact antibody or antigen binding fragment thereof of the SEQ ID NO recited in instant claim 5.

Evidentiary reference Davies and Riechmann (Biotechnology, 13: 475-479, 1995, of record) teach the importance of all three CDR loops in V_HH antibodies for binding antigen.

There is no description in the specification as to what alterations result in a functional antibody or fragment thereof that binds specifically to human pancreatic lipase and comprises one of the SEQ ID NO recited in instant claim 4, except for the antibodies or antigen binding fragments thereof of the SEQ ID NO recited in instant claim 5 that have all three CDR regions of the heavy chain.

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in Applicant's response filed 1/29/07 on page 5.

It is the Examiner's position that the recitation in instant claim 4 of an antibody or fragment thereof that specifically binds human pancreatic lipase, said antibody or fragment thereof comprising three CDR, whereby a CDR3 is one of the recited SEQ ID NO, is not sufficient to demonstrate possession of the claimed antibody or fragment thereof because the other two CDR contribute to the specificity of the antibody or fragment thereof. The instant specification does not disclose the definition of "a heavy chain variable domain derived from an immunoglobulin naturally devoid of light chains" recited in instant claim 1, and so the recited limitation may encompass less than the entire variable region of a V_HH antibody. In addition, the antibody or fragment thereof recited in instant claim 4 comprising 3 CDR regions, the CDR3 region having a sequence recited in instant claim 4, does not recite that the 3 CDR regions must be a combination of CDR1, CDR2 and CDR3.

5. Claims 1, 4, 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and/or use the instant invention: (1) the claimed antibody or fragment thereof that binds specifically to a human pancreatic lipase and wherein the antibody or fragment thereof of comprises a variable domain derived from an immunoglobulin naturally devoid of light chains, and food product thereof or pharmaceutical composition thereof, recited in the instant claims, (2) the claimed antibody or fragment thereof recited in instant claim 4 wherein the antibody or fragment thereof that binds one or more human pancreatic lipases comprises 3 CDR regions, whereby CDR3 is one of the recited SEQ ID NO and wherein the antibody or fragment thereof of comprises a variable domain derived from an immunoglobulin naturally devoid of light chains, and the antibody or fragment thereof is not one of the full length antibody sequences or antigen binding fragments thereof of the SEQ ID NO recited in instant claim 5.

The specification has not enabled the breadth of the claimed invention because the claims encompass: an antibody or fragment thereof that specifically binds human pancreatic lipase and comprises a CDR3 from the sequences recited in instant claim 4 and has undisclosed other portions that may not be CDR1 and CDR2, or that comprises some domain from a heavy chain variable region as recited in instant claim 1 that may or may not be a CDR. There is insufficient disclosure in the specification on such an antibody/fragment/functional equivalent/composition thereof wherein the antibody or fragment comprises a heavy chain variable domain derived from an immunoglobulin naturally devoid of light chains, wherein the entire variable region of a V_HH antibody is not present. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed antibody/fragment and food product and composition thereof wherein the antibody or fragment comprises a V_HH can be made and/or used.

The specification discloses that it is desirable to decrease the level of LDL and that several dietary enzymes may be involved in the hydrolysis reaction that liberates fatty acids in the GI tract to increase the adsorption of cholesterol by the epithelium (page 1). The specification discloses that other enzymes in the GI tract may be involved in undesirable physiological reactions and examples of such enzymes, referred to as human dietary enzymes, include oxidoreductases, transferases, hydrolases (*e.g.,* lipases, proteolytic enzymes and ureases), lyases, isomerases and ligases or synthetases (page 2 at lines 1-5). The specification discloses that human pancreatic lipase (HPL) was purified, used as an immunogen to generate V_HH antibodies in a llama, and V_HH fragments that inhibited HPL were cloned, selected, screened, enriched, a portion were sequenced, and the V_HH were grouped into three classes depending upon the length of CDR3 (pages 15-24). The specification further discloses that a

number of these were re-cloned and purified (pages 25-26). The specification discloses parallel work for production of V_HH antibodies to human gastric lipase (HGL) (pages 28-32). The specification discloses feeding the antibodies HPL18 and HGL8 to piglets in combination with a high fat diet, and that in 2/3 animals, the antibodies inhibited fat digestion and uptake as evidenced by a reduction in blood triglyceride levels (pages 33-36). The specification further discloses that the V_HH antibodies are used for the inhibition, or in the case of human dietary lipases for partial inhibition, of the enzymes involved in the hydrolysis of dietary fats (pages 8 at lines 28-31, page 9 at lines 23-30 and the brief description of the drawings for Figures 1-3, figures 1-3).

The specification does not disclose antibodies comprising just a CDR3 region peptide recited in instant claim 4 without the corresponding other CDR1 and CDR2 regions, including those that accompany them in the intact antibody or antigen binding fragment thereof of the SEQ ID NO recited in instant claim 5.

Evidentiary reference Davies and Riechmann (Biotechnology, 13: 475-479, 1995, of record) teach the importance of all three CDR loops in V_HH antibodies for binding antigen.

The specification does not disclose antibodies comprising just the CDR3 regions peptides recited in instant claim 4 without the corresponding other CDR1 and CDR2 regions, including those that accompany them in the intact antibody or antigen binding fragment thereof of the SEQ ID NO recited in instant claim 5, nor making an antibody starting from just the CDR3 regions peptides recited in instant claim 4. Hence it is unpredictable if the antibodies can be made and/or used.

There is no guidance in the specification as to what alterations result in a functional antibody or fragment thereof that binds specifically to a human pancreatic lipase, or a functional antibody or fragment thereof that binds specifically to human pancreatic lipase and comprises some domain of a heavy chain variable region, including comprises a SEQ ID NO recited in instant claim 4, without the corresponding CDR1 and CDR2 regions of the heavy chain variable region. Because of this lack of guidance, the extended experimentation that would be required to determine which additions would be acceptable to retain functional activity of binding specifically to human pancreatic lipase, especially as the fact that the relationship between the sequence of a peptide and its tertiary structure (*i.e.,* its activity) are not well understood and are therefore not predictable (Ngo *et al.* The Protein Folding Problem and Tertiary Structure Prediction, Merz & LeGrand, Birkhauser Boston, pages 491-495, 1994, entire article, especially Section 6, paragraph 1, of record), it would require undue experimentation for one of skill in the art to arrive at other amino acid sequences that would have functional activity. In other words, since it would require undue experimentation to identify amino acid sequences that have functional activity, it would require undue experimentation to make and use the corresponding sequences.

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in Applicant's response filed 1/29/07 on page 6 at the first full paragraph.

It is the Examiner's position that the issue is not that the claim is not limited to the specifically disclosed CDR1 and CDR2 regions, but that the recitation in instant claim 4 of an antibody or fragment thereof that specifically binds human pancreatic lipase, said antibody or fragment thereof comprising three CDR, whereby a CDR3 is one of the recited SEQ ID NO, is not sufficient to demonstrate possession of the claimed antibody or fragment thereof because the other two CDR contribute to the specificity of the antibody or fragment thereof, and the claim does not recite that the 3 CDR regions must be a combination of CDR1, CDR2 and CDR3. The instant specification does not disclose the definition of "a heavy chain variable domain derived from an immunoglobulin naturally devoid of light chains" recited in instant claim 1, and so the recited limitation may encompass less than the entire variable region of a V_HH antibody.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/34630 (IDS reference) in view of Aoubala *et al* (J. Biol. Chem. 8: 3932-3937, 1995, IDS reference), STN Accession Number: 1998286804 EMBASE (of record), WO 99/46300 (IDS reference), U.S. Patent No. 6,558,936 B1 (of record) and Lauwereys *et al* (The EMBO Journal, 13: 3512-3520, 1998, of record).

WO 98/34630 teaches use of a gastrointestinal lipase inhibitor in oral medicaments for treating type II diabetes mellitus and for the control of obesity and hyperlipidemia.

WO 98/34630 does not teach medicaments comprising an antibody, or fragment thereof, capable of binding specifically to a human dietary lipase, including HPL, said antibody or fragment thereof comprising a V_HH.

Aoubala *et al* teach anti-HPL mAbs that inhibit the lipolytic activity of HPL.

STN Accession Number: 1998286804 EMBASE teaches that inhibition of pancreatic lipase offers the opportunity to intensify the weight reducing effect of diet, and that obesity increases risk of type II diabetes mellitus.

WO 99/46300 teaches that V_HHs are comparable to mouse monoclonal antibodies in terms of specificity, high affinity but are more stable against destabilizing physical and/or chemical conditions, including under pasteurization conditions, than traditional antibodies and that it is therefore advantageous to use them in food products. WO 99/46300 teaches food products include ice cream, oils, margarines, dressings, drinks and meals. WO 99/46300 teaches that V_HHs have superior stability, specificity and affinity as compared to mouse mAbs, characteristics that make them excellent candidates for use in existing and novel applications. WO 99/46300 teaches that V_HHs can be produced that bind specifically to and neutralize enzymes that are present (especially page 20). WO 99/46300 teaches methods of making V_HHs. WO 99/46300 teaches preparing, storing or using V_HHs in food products under conditions wherein pH is less than 5. WO 99/46300 teaches selecting suitable V_HHs under the destabilizing conditions which the product is made, stored and/or used to select V_HHs that are most stable under the said conditions (see entire document, especially paragraph spanning pages 5-6, paragraph spanning pages 13-15, page 16 at lines 16-28, claims 1, 2, 11, 12 and 22).

U.S. Patent No. 6,558,936 B1 discloses use of antagonists, including antibodies in therapeutic pharmaceutical compositions to inhibit the activity of a lipase protein. U.S. Patent No. 6,558,936 B1 further discloses that dietary lipids are taken up primarily by hydrolysis of fatty acyl moieties from their corresponding polyol moiety and this reaction is catalyzed by lipases, followed by diffusion across the gut wall (especially column 1 at lines 16-42). U.S. Patent No. 6,558,936 B1 discloses that antibodies to the said lipase protein, and disclose that said lipase protein has activity similar or identical to human pancreatic lipase, are useful for treating hyperlipidemia, atherosclerosis, diabetes and obesity (especially column 3 at lines 45-64, column 10 at lines 55-63, column 48 at lines 42-69, and columns 49 and 50). U.S. Patent No. 6,558,936 B1 discloses routes of administration of pharmaceutical compositions, including the modulating antibodies or F(ab) or F(ab')2 fragments thereof, include IV, ID, SC, oral and TD (especially column 5 at lines 49-58, column 22 at lines 36-58, column 31 at lines 45-67, column 32 at lines 1-23, column 33 at lines 32-62). U.S. Patent No. 6,558,936 B1 discloses use of the antibodies in *in vitro* assays for detecting activity of a lipase (especially column 4 at lines 44-55).

Lauwereys *et al* teach that heavy chain antibodies, *i.e.,* V_HH, are a unique source of inhibitory antibodies superior to conventional antibodies. Lauwereys *et al* teach that the number of conventional four-chain antibodies consisting of two light and two heavy chains that act as competitive enzyme inhibitors is low, an outcome that is explained by the incompatible surface topography of the enzyme's active site and the antigen binding site of conventional antibodies. Lauwereys *et al* teach that occasionally, conventional antibodies are able to inhibit enzymatic activity, however, these are more the exception than the rule. Lauwereys *et al* teach that the heavy chain antibodies have acquired the potential to recognize protein cavities, and as such, the ability to inhibit enzymes. Lauwereys *et al* exemplify immunization of a dromedary with enzymes of disparate sequence and demonstrate a substantial proportion of the heavy chain antibodies bind into the active site of the enzymes and inhibit their activity in a concentration-dependent manner. Lauwereys *et al* teach that for each target enzyme, the cloned V_HH repertoire use different CDR sequences. Lauwereys *et al* teach that the V_HH possess superior properties such as simple isolation, high solubility and stability, and that the cloning and expression of V_HH antibody fragments is a general and powerful strategy to obtain a new type of potent and specific enzyme inhibitor in a short time period. Lauwereys *et al* teach *in vitro* testing of the heavy chain antibodies for concentration dependent inhibition of enzymes. Lauwereys *et al* teach that heavy chain antibodies are likely to be superior to scFv constructs (especially abstract, introduction, and discussion).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used a V_HH version of a neutralizing anti-enzyme V_HH antibody as taught by WO 99/46300 and as taught by Lauwereys *et al* having the specificity of an anti-human pancreatic lipase (anti-HPL) antibody such as that taught by Aoubala *et al* in the oral pharmaceutical composition taught by WO 98/34630 or a food product such as taught by WO 99/46300 to inhibit pancreatic lipase as taught by WO 98/34630, STN Accession Number: 1998286804 EMBASE and by U.S. Patent No. 6,558,936 B1 for pancreatic lipase. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the anti-HPL V_HH in *in vitro* assays for assessing the activity of the HPL/antibody as taught by Lauwereys *et al* for testing efficacy of the heavy chain antibodies and as disclosed by U.S. Patent No. 6,558,936 B1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat obesity and/or diabetes mellitus type II as taught by WO 98/34630 and by STN Accession Number: 1998286804 EMBASE using a more stable version of the neutralizing anti-HPL mAbs taught by Aoubala *et al* or polyclonal anti-HPL antibodies, such as the V_HHs taught by WO 99/46300 and by Lauwereys *et al,* since WO 99/46300 teaches the advantage of using them in food products, Lauwereys *et al* teach V_HH superiority in terms of enzyme inhibition, stability, solubility and simple isolation or production, and U.S. Patent No. 6,558,936 B1 discloses use of antagonists, including antibodies in therapeutic pharmaceutical compositions to inhibit the activity of a lipase. One of ordinary skill in the art at the time the invention was made would have

been motivated to do this in order to test the efficacy of the antibodies prior to administering them *in vivo*. With regard to the inclusion of claim 10 in this rejection, the combined invention is a pharmaceutical product since it is being administered to a subject *in vivo*, and U.S. Patent No. 6,558,936 B1 discloses pharmaceutical compositions comprising lipase-inhibiting antibodies.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in Applicant's amendment filed and response filed 1/29/06 (on pages 6-7).

It is the Examiner's position that WO 99/46300 teaches manufacture, storage and use of V_HHs in products, including food products, under conditions comparable to that in the GI tract of a mammal, *i.e.,* at pH less than 5, as well as a selection step for selecting the most stable V_HHs under the destabilizing conditions for manufacture, storage and use. In addition, U.S. Patent No. 6,558,936 B1 discloses oral routes of administration of lipase inhibiting antibodies, in contrast to Applicant's assertion that a distinction should be made between antibodies that can be used for detection purposes *in vitro* and antibodies that inhibit lipase activity *in vivo* under adverse conditions such as those in the GI tract in a mammal. Lauwereys *et al* teach that heavy chain antibodies are uniquely suited to binding to the active site of enzymes, one of three mechanisms that Applicant had argued in the last response as being applicable to antibody inhibition of lipases. Applicant does not provide evidence of which effector functions are lacking in V_HHs *vs* traditional antibodies, nor evidence that those effector functions diminish the ability of V_HHs to inhibit enzyme activity. With regard to Applicant's arguments to US 6,558,936, it is the Examiner's position that '936 is being argued separately by Applicant. Although '936 discloses that for therapeutic treatment of humans, human antibodies are preferred, it also discloses that chimeric antibodies are also within the scope of the invention, and both WO 99/46300 and Lauwereys *et al* teach the surperiority of V_HHs over traditional antibodies that are four chain immunoglobulins such as human, humanized or chimeric, Lauwereys *et al* with respect to being superior as inhibitory antibodies over conventional four chain antibodies. It is the Examiner's position that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention for the reasons enunciated in the instant rejection and in the Examiner's position enunciated herein.

8. Claims 1, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,558,936 B1 (of record) in view of Aoubala *et al* (J. Biol. Chem. 8: 3932-3937, 1995, IDS reference), WO 99/46300 (IDS reference) and Lauwereys *et al* (The EMBO Journal, 13: 3512-3520, 1998, of record).

U.S. Patent No. 6,558,936 B1 discloses use of antagonists, including antibodies in therapeutic pharmaceutical compositions to inhibit the activity of a lipase protein. U.S. Patent No. 6,558,936 B1 further discloses that dietary lipids are taken up primarily by hydrolysis of fatty acyl moieties from their corresponding polyol moiety and this reaction is catalyzed by lipases, followed by diffusion across the gut wall (especially column 1 at lines 16-42). U.S. Patent No. 6,558,936 B1 discloses that antibodies to the said lipase protein are useful for treating hyperlipidemia, atherosclerosis, diabetes and obesity (especially column 3 at lines 45-64, column 48 at lines 42-69 and columns 49 and 50). U.S. Patent No. 6,558,936 B1 discloses routes of administration of pharmaceutical compositions, including the modulating antibodies or F(ab) or F(ab')2 fragments thereof, include IV, ID, SC, oral and TD (especially column 5 at lines 49-58, column 22 at lines 36-58, column 31 at lines 45-67, column 32 at lines 1-23, column 33 at lines 32-62). U.S. Patent No. 6,558,936 B1 discloses use of the antibodies in *in vitro* assays for detecting activity of a lipase (especially column 4 at lines 44-55). U.S. Patent No. 6,558,936 B1 does not disclose a pharmaceutical or food composition comprising an antibody, or fragment thereof, capable of binding specifically to one or more human dietary enzymes, said antibody or fragment thereof comprising a V_HH, nor wherein the antibody or fragment thereof or functional equivalent is capable of specifically binding human pancreatic lipase (HPL).

Aoubala *et al* teach anti-HPL mAbs that inhibit the lipolytic activity of HPL.

WO 99/46300 teaches that V_HHs are comparable to mouse monoclonal antibodies in terms of specificity, high affinity but are more stable against destabilizing physical and/or chemical conditions, including under pasteurization conditions, than traditional antibodies and that it is therefore advantageous to use them in food products. WO 99/46300 teaches food products include ice cream, oils, margarines, dressings, drinks and meals. WO 99/46300 teaches that V_HHs have superior stability, specificity and affinity as compared to mouse mAbs, characteristics that make them excellent candidates for use in existing and novel applications. WO 99/46300 teaches that V_HHs can be produced that bind specifically to and neutralize enzymes that are present (especially page 20). WO 99/46300 teaches methods of making V_HHs. WO 99/46300 teaches preparing, storing or using V_HHs in food products under conditions wherein pH is less than 5. WO 99/46300 teaches selecting suitable V_HHs under the destabilizing conditions which the product is made, stored and/or used to select V_HHs that are most stable under the said conditions (see entire document, especially paragraph spanning pages 5-6, paragraph spanning pages 13-15, page 16 at lines 16-28, claims 1, 2, 11, 12 and 22).

Lauwereys *et al* teach that heavy chain antibodies, *i.e.,* V_HH, are a unique source of inhibitory antibodies superior to conventional antibodies. Lauwereys *et al* teach that the number of conventional four-chain antibodies consisting of two light and two heavy chains that act as competitive enzyme inhibitors is low, an outcome that is explained by the incompatible surface topography of the enzyme's active site and the antigen binding site of conventional antibodies. Lauwereys *et al* teach that occasionally, conventional antibodies are able to inhibit enzymatic activity, however, these are more the exception than the rule. Lauwereys *et al* teach that the heavy chain antibodies have acquired the potential to recognize protein cavities, and as such, the ability to inhibit enzymes. Lauwereys *et al* exemplify immunization of a dromedary with enzymes of disparate sequence and demonstrate a substantial proportion of the heavy chain antibodies bind into the active site of the enzymes and inhibit their activity in a concentration-dependent manner. Lauwereys *et al* teach that for each target enzyme, the cloned V_HH repertoire use different CDR sequences. Lauwereys *et al* teach that the V_HH possess superior properties such as simple isolation, high solubility and stability, and that the cloning and expression of V_HH antibody fragments is a general and powerful strategy to obtain a new type of potent and specific enzyme inhibitor in a short time period. Lauwereys *et al* teach *in vitro* testing of the heavy chain antibodies for concentration dependent inhibition of enzymes. Lauwereys *et al* teach that heavy chain antibodies are likely to be superior to scFv constructs (especially abstract, introduction, and discussion).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used a V_HH version as taught by WO 99/46300 and by Lauwereys *et al* of an inhibiting anti-HPL antibody such as that taught by Aoubala *et al* in the pharmaceutical composition disclosed by U.S. Patent No. 6,558,936 B1 to inhibit pancreatic lipase as disclosed by U.S. Patent No. 6,558,936 B1 for another pancreatic lipase. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made an anti-HPL V_HH antibody and tested it in an *in vitro* assay for it's ability to inhibit HPL as taught by Lauwereys *et al* for the enzyme-inhibiting V_HH antibodies.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat obesity and/or diabetes mellitus type II as taught by U.S. Patent No. 6,558,936 B1 using a more stable version of the neutralizing anti-HPL mAbs taught by Aoubala *et al* such as the V_HHs taught by WO 99/46300 since WO 99/46300 teaches that the advantage of using them include higher stability and affinity, particularly under destabilizing conditions. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to test the efficacy of the antibodies prior to administering them *in vivo*.

With regard to the inclusion of claim 9 in this rejection, WO 99/46300 teaches the advantage of using V_HHs in food preparations, and since U.S. Patent No. 6,558,936 B1 discloses the first site of lipase action is in the lumen of the gut, it would have been obvious to include the antibody in an oral pharmaceutical preparation or a food product such as those taught by WO 99/46300 for use with other V_HHs. In addition, Lauwereys *et al* teach the superiority of V_HH in terms of enzyme inhibition, stability, solubility and simple isolation or production, and U.S. Patent No. 6,558,936 B1 discloses use of antagonists, including antibodies in therapeutic pharmaceutical compositions to inhibit the activity of a lipase protein. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to test the efficacy of the antibodies prior to administering them *in vivo*.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in Applicant's amendment filed and response filed 1/29/06 (on pages 6-7).

It is the Examiner's position that WO 99/46300 teaches manufacture, storage and use of V_HHs in products, including food products, under conditions comparable to that in the GI tract of a mammal, *i.e.,* at pH less than 5, as well as a selection step for selecting the most stable V_HHs under the destabilizing conditions for manufacture, storage and use. In addition, U.S. Patent No. 6,558,936 B1 discloses oral routes of administration of lipase inhibiting antibodies, in contrast to Applicant's assertion that a distinction should be made between antibodies that can be used for detection purposes *in vitro* and antibodies that inhibit lipase activity *in vivo* under adverse conditions such as those in the GI tract in a mammal. Lauwereys *et al* teach that heavy chain antibodies are uniquely suited to binding to the active site of enzymes, one of three mechanisms that Applicant had argued in the last response as being applicable to antibody inhibition of lipases. Applicant does not provide evidence of which effector functions are lacking in V_HHs *vs* traditional antibodies, nor evidence that those effector functions diminish the ability of V_HHs to inhibit enzyme activity. With regard to Applicant's arguments to US 6,558,936, it is the Examiner's position that '936 is being argued separately by Applicant. Although '936 discloses that for therapeutic treatment of humans, human antibodies are preferred, it also discloses that chimeric antibodies are also within the scope of the invention, and both WO 99/46300 and Lauwereys *et al* teach the surperiority of V_HHs over traditional antibodies that are four chain immunoglobulins such as human, humanized or chimeric, Lauwereys *et al* with respect to being superior as inhibitory antibodies over conventional four chain antibodies. It is the Examiner's position that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention for the reasons enunciated in the instant rejection and in the Examiner's position enunciated herein.

9. Claim 5 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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